Transfusion-Associated Graft-Versus-Host Disease in Severe Combined Immunodeficiency

S Sebnem Kilic,[1] S Kavurt,[1] S Balaban Adim[2]

[1]Department of Pediatric Immunology, Uludag University, School of Medicine, Bursa, Turkey
[2]Department of Pathology, Uludag University, School of Medicine, Bursa, Turkey

Abstract

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare complication of cellular blood component transfusion that produces a graft-versus-host clinical picture with concomitant bone marrow aplasia. We report the case of 2 patients with severe combined immunodeficiency (SCID) who developed TA-GvHD. Both patients had been given nonirradiated erythrocyte suspension before the diagnosis of SCID. Although one of them was aged 12 months, he had still not been diagnosed as having severe T-cell deficiency at the time of transfusion. Both patients presented similar signs and symptoms (fever, skin rash, diarrhea, pancytopenia, and icterus). Skin biopsies demonstrated Grade II GVHD involvement. In both cases, sepsis and septic shock developed, with progression to multiorgan failure. Unfortunately, the 2 patients died, despite prompt, appropriate sepsis treatment and immunomodulatory therapy. TA-GVHD must be considered in the differential diagnosis of patients who present fever, pancytopenia, diarrhea, skin rash and icterus, and the transfusion history must be questioned.

Key words: Transfusion-associated graft-versus-host disease. Severe combined immunodeficiency. Irradiation. Skin biopsy.

Resumen

La enfermedad injerto contra huésped asociada a transfusión (EICH-AT) es una complicación poco común de la transfusión de componentes sanguíneos que produce un cuadro clínico de injerto contra huésped con aplasia medular concomitante. Se presenta el caso de dos pacientes con inmunodeficiencia combinada grave (IDCG) que desarrollaron EICH-AT. Ambos pacientes habían recibido una suspensión de eritrocitos no irradiada antes del diagnóstico de IDCG. Aunque uno de ellos tenía 12 meses de edad, todavía no se le había diagnosticado un déficit grave de linfocitos T en el momento de la transfusión. Ambos pacientes presentaron signos y síntomas similares (fiebre, erupción cutánea, diarrea, pancitopenia e ictericia). Las biopsias cutáneas demostraron la presencia de EICH de grado II. En ambos casos se desarrolló sepsis y choque septicémico que progresaron a insuficiencia multiorgánica. Desafortunadamente, ambos pacientes fallecieron a pesar de haber recibido con prontitud un tratamiento para la sepsis y una terapia inmunomoduladora adecuados. La EICH-AT debe considerarse en el diagnóstico diferencial de los pacientes que presentan fiebre, pancitopenia, diarrea, erupción cutánea e ictericia, y también deben cuestionarse los antecedentes de transfusiones.

Palabras clave: Enfermedad injerto contra huésped asociada a transfusión. Inmunodeficiencia combinada grave. Irradiación. Biopsia cutánea.

Introduction

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare complication of the transfusion of nonirradiated cellular blood components in susceptible recipients. It results from the engraftment of transfused immunocompetent T cells in blood transfusion recipients whose immune system is unable to reject them. Engrafted donor T cells mediate a cellular immune response against host tissues, resulting in damage to the skin, liver (hepatitis), gastrointestinal tract, and bone marrow [1]. Major risk factors for the development of TA-GVHD are congenital immunodeficiency syndromes, bone marrow transplantation, transfusion from descendant relatives, intrauterine transfusions, and human leukocyte antigen–matched platelet transfusions. The disease is fulminant and rapidly fatal in the majority of immunocompromised patients.

Treatment is generally not helpful, while prevention, usually via the irradiation of blood components given to susceptible recipients, is the key to obviating TA-GVHD [2].

We report the case of 2 patients with severe combined immunodeficiency (SCID) that developed TA-GVHD and also review the literature. Both patients received nonirradiated, fresh erythrocyte suspension from unrelated donors.

Case Description

Case 1

This 2-month-old boy was the sixth offspring of a first degree-consanguineous marriage. His history included admission to another hospital for the treatment of pneumonia 1 month before arrival at our hospital. The treatment had included transfusion of a unit of nonirradiated erythrocyte suspension from an unrelated donor. He was referred to our department with suspected immunodeficiency in the second week after the transfusion. Two male children of the parents had died because of recurrent infections when they were 2 and 3 months old. Physical examination revealed that the patient had a fever of 37.8ºC and a pulse of 107 bpm. His weight and height were between the fifth and tenth percentile. We also observed disseminated erythematous squamous skin rash (Figure) and severe oral mucositis. Auscultation of the chest revealed bilateral crepitating rales in both lung fields. Laboratory findings are given in Table 1. The patient showed hypogammaglobulinemia and very low counts of $CD3^+$ and $CD19^+$ cells; natural killer (NK) cell count was normal (Table 2). He was diagnosed as having $T^-B^-NK^+$ SCID. The chest x-ray showed bilateral reticular infiltration of lung fields. Cefepime, teicoplanin, and fluconazole were started intravenously for pulmonary infection and the patient was already receiving 3-weekly intravenous immunoglobulin therapy. Molecular analysis of *Rag1*, *Rag2*, and *Artemis* did not show any mutations.

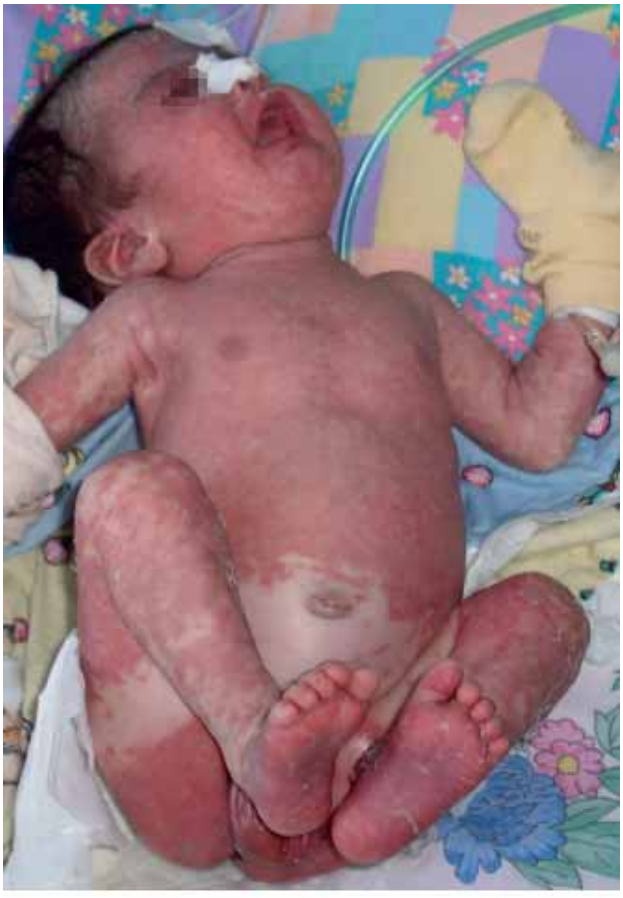

Figure. Skin involvement of a patient with severe combined immunodeficiency who developed transfusion-associated graft versus host disease.

Table 1. Clinical Characteristics

Characteristics	Patient 1	Patient 2
Age, mo	2	13
Sex	Male	Male
Transfused blood, units	1	2
Fever onset, d[a]	10	12
Rash onset, d[a]	10	12
Diarrhea	Not bloody	Not bloody
Hemoglobin, g/dL (normal, 12-16 g/dL)	7.6	7
Hematrocrit, % (normal, 36%-54%)	22	21
White blood count, x10 (normal, 3.6-10)	200	1200
Platelets, 10/L (normal 150-450/L)	215	56
Alanine transaminase, IU/mL (normal, 5-40 IU/mL)	190	340
Aspartate transaminase, IU/mL (normal, 8-33 IU/mL)	425	225
Total bilurubin, mg/dL (normal, 0.0-1.2 mg/dL)	3.2	2.6
Cause of death	Septic shock	Septic shock

[a] After transfusion.

On the eighth day of admission, a generalized maculopapular rash appeared, the patient became febrile (39ºC), and the liver was palpable 3 cm below the right costal margin. Serum transaminase levels were markedly elevated and γ-glutamyltransferase was 515 IU/L. On day 10, pancytopenia and diarrhea developed. Severe skin eruptions, abnormal serum transaminase levels, fever, severe pancytopenia, and the history of blood transfusion suggested TA-GVHD. A skin biopsy performed to confirm the diagnosis showed basal vacuolar degeneration, necrotic-apoptotic keratinocytes, and lymphocytic infiltration, all compatible with grade II GVHD. High-dose methylprednisolone (10 mg/kg for 3 days, 5 mg/kg for 3 days), intravenous immunoglobulin (1 g/kg), and cyclosporin (5 mg/kg) were used for the treatment. Extended-spectrum

Table 2. Immunologic Parameters

	Patient 1	Normal	Patient 2	Normal
Absolute lymphocyte count, mm^3	300	3700-9600	450	2600-10400
Immunoglobulin (Ig) G, mg/dL	173	294-1165[a]	<146	605-1430
IgM, mg/dL	<16.8	33-154	58	66-228
IgA, mg/dL	<25.4	13.5-72	<21.8	30-107
$CD3^+$ T cells, % (absolute count/mm^3)	0.53 (0.17)	48-75 (2400-6900)	0.9 (0.2)	54-76 (1600-6700)
$CD19^+$ B cells, % (absolute count/mm^3)	0	14-39 (600-3000)	50.8 (11.2)	15-39 (600-2700)
$CD4^+$ helper T cells, % (absolute count/mm^3)	2.3 (0.76)	33-58 (1500-5000)	0.5 (0.1)	31-54 (1000-4600)
$CD8^+$ suppressor T cells, % (absolute count/mm^3)	21.4 (7.1)	11-25 (500-1600)	0.3 (0.06)	12-28 (400-2100)
Natural killer cells $CD3^-CD16^+CD56$, % (absolute count/mm^3)	88.9 (29.6)	2-14 (100-1300)	43.7 (9.7)	3-17 (200-1200)

[a]Normal serum Ig levels for the ages of the patients was defined according to the Turkish reference values for healthy Turkish children.

antibiotics (meropenem, 40 mg/kg every 8 hours and amikacin, 15 mg/kg/d), antifungal (amphotericin B, 3 mg/kg), and antiviral agents (gancyclovir, 10 mg/kg every 8 hours) were needed for the overwhelming infections. In addition, irradiated packed red blood cells, fresh frozen plasma, and thrombocyte suspension were used for supplementary therapy. Despite the intense treatment, multiorgan failure developed and the patient died on the 40th day of admission.

Case 2

A 12-month-old boy was admitted to a government children's hospital because of failure to thrive, recurrent otitis media, and respiratory tract infections since 4 months old. Because of his poor general condition and anemia, he was transfused with 2 units of nonirradiated erythrocytes (day 1 and 3). Ten days later, agammaglobulinemia was detected and the patient was transferred to our hospital. His older brother had died of pulmonary infection and sepsis when he was 4 months old. There was no parental consanguinity. On the second day of admission, physical examination revealed a fever of 38.5ºC (axillary) and a pulse of 120 bpm. There was pallor, disseminated erythematous squamous skin rash, hepatomegaly, severe oral mucositis, and diarrhea. The first laboratory studies revealed anemia and leukopenia and impaired liver functions. Serum immunoglobulin (Ig) G and IgA levels and T-cell subsets were very low (Table 2). A diagnosis of X-linked SCID, with a $T^-B^+NK^+$ phenotype was made. Molecular analysis of the IL-7Rα and CD3 Rγ genes revealed no mutations. In the view of the fact that the patient was immunocompromised and developed pancytopenia, maculopapuler erythematous rash, fever, and diarrhea following transfusion, the diagnosis was TA-GVHD. A skin biopsy was performed, which revealed mononuclear cell infiltration at the dermis, epithelial vacuolization, and increased fibroblastic activity. These findings were compatible with GVHD. Treatment with broad-spectrum antibiotics was started for febrile neutropenia. Methlyprednisolone (2 mg/kg/d) and cylosporin (7 mg/kg/d) treatments were also begun and the patient was put on 3-weekly intravenous Ig treatment. The skin lesions and mucositis disappeared and transaminases dropped to normal levels in 2 weeks. On the 40th day of admission, the generalized erythematous maculopapuler rash reappeared, accompanied by the development of pancytopenia, diarrhea, and hepatomegaly. Blood culture showed Klebsiella pneumaniae infection. In addition to broad-spectrum antibiotics and amphotericin B for febrile neutropenia, granulocyte colony-stimulating factor was started. Antithymocyte globulin (5 mg/kg/dose was given intravenously). Nonetheless, the diarrhea persisted and the serum transaminase levels increased dramatically. The patient died of multiorgan failure on the 90th day of admission.

Discussion

GVHD is an infrequent complication of blood transfusions, with an incidence of 0.1% to 1%. TA-GVHD has a high mortality rate in immunocompromised patients due to impaired elimination of alloreactive, erythrocyte transfusion-derived lymphocytes [3,4]. In susceptible patients, whether they are immunocompetent or have congenital or acquired cellular immune deficiency, transfused T cells are not destroyed; instead, they proliferate and can induce an immune response which rejects the host tissues. Usually, the fatal outcome of TA-GVHD can be explained by the delay in diagnosis of the underlying immunodeficiency and therefore delayed institution of immunosuppressive therapy [2]. Both of our patients were given nonirradiated

erythrocyte suspension before the diagnosis of SCID. Although one of them was 1-year-old, he had still not been diagnosed as having severe T-cell deficiency at the time of transfusion. Early identification of affected patients, i.e. before the development of disease-related problems, is critical to a successful outcome. A complete blood count with differential should be analyzed first. Persistent lymphopenia can be a sign of cellular immunodeficiency. Lymphopenia is defined as fewer than 3000 cells/mm^3 (normal range in infants). A diagnosis of SCID is suggested when an infant has lymphopenia, a CD3$^+$ T cell count of less than 20%, and severe hypogammaglobulinemia (IgG, <150 mg/dL) [5].

Congenital cellular immunodeficiency has been associated with TA-GVHD, not only in patients with severe combined immunodeficiency, but also in those with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia, and purine nucleoside phosphorylase deficiency [6-11]. There have been no cases reported of patients with primary immunodeficiency and GVHD since the last report in 2003 of a patient with SCID who developed TA-GVHD [12].

The diagnosis of TA-GVHD is based on the evaluation of clinical manifestations in combination with relevant laboratory findings, where the gold standard tests are biopsy of the skin and liver or a bone marrow aspirate [4]. The most commonly affected organ systems in TA-GVHD are the skin, liver, and intestines. Febrile illness and skin manifestations are the usual initial presenting signs of GVHD. Skin lesions can range from erythematous macules to hemorrhagic bullae. Fever is the first symptom, with an average onset of 10 days after transfusion. After fever, an erythematous maculopapular skin rash appears on the trunk and spreads to the palms and soles. Associated gastrointestinal problems are elevated liver enzymes, often with associated hepatomegaly and jaundice, in addition to gastrointestinal symptoms, including nausea, vomiting, and diarrhea [3]. Within 2 weeks of tranfusion, our patients developed a disseminated erythematous squamous skin rash, fever, abnormal liver function, diarrhea, and wasting. The results of the skin biopsy were compatible with grade II GVHD.

The most important differences between TA-GVHD and post-transplant GVHD are bone marrow hypoplasia, pancytopenia, and an increased risk of infection and hemorrhage [1]. Most patients die within 1 month of transfusion. Our patients died on day 40 and day 60 after admission, despite aggressive treatment.

TA-GVHD is unresponsive to immunosuppressive therapy and mortality exceeds 90%. It has been reported that leukoreduction does not completely eliminate the risk of TA-GVHD. Irradiation of blood products, which inhibits the proliferation of donor lymphocytes, is necessary for prevention with a preferred irradiation dose of 2500 cGy [13]. Newer methods, such as pathogen inactivation, may play an important role in the future.

TA-GVHD is still encountered in SCID patients today after the transfusion of nonirradiated blood products. Prompt recognition of the condition and avoidance of nonirradiated blood products and live vaccines are life-saving precautions. Prevention remains the key to reducing the incidence of TA-GVHD.

Acknowldegements

We thank Anna Villa, from Milan, Italy and Silvia Giliani, from Brescia, Italy, for their kind help in performing molecular analysis of the genes analyzed.

References

1. Dwyre DM, Holland PV. Transfusion-associated graft-versus-host disease. Vox Sang. 2008;95:85-93.
2. Agbaht K, Altintas ND, Topeli A, Gokoz O, Ozcebe O. Transfusion-associated graft-versus-host disease in immunocompetent patients: case series and review of the literature. Transfusion. 2007;47: 1405-11.
3. Seghatchian MJ, Ala F. Transfusion-associated graft-versus-host disease: current concepts and future trends. Transfus Sci. 1995;16:99-105.
4. Rühl H, Bein G, Sachs UJ. Transfusion-associated graft-versus-host disease. Transfus Med Rev. 2009;23: 62-71.
5. Elder ME. T cell immunodeficiencies. Pediatr Clin North Am. 2000;47:1253-74.
6. Park BH, Good RA, Gate J, Burke B. Fatal graft-vs.-host reaction following transfusion of allogeneic blood and plasma in infants with combined immunodeficiency disease. Transplant Proc 1974;6:385-7.
7. Brouard J, Morin M, Borel B, Laloum D, Mandard JC, Duhamel JF, Venezia R. Di George's syndrome complicated by graft versus host reaction. Arch Fr Pediatr. 1985;42:853-5.
8. Wintergerst U, Meyer U, Remberger K, Belohradsky BH. Graft versus host reaction in an infant with DiGeorge syndrome. Monatsschr Kinderheilkd. 1989;137:345-7.
9. Douglas SD, Fudenberg HH. Graft versus host reaction in Wiskott-Aldrich syndrome: antemortem diagnosis of human GVH in an immunologic deficiency disease. Vox Sang. 1969;16:172-8.
10. Watson HG, McLaren KM, Todd A, Wallace WH. Transfusion associated graft-versus-host disease in ataxia telangiectasia. Lancet. 1997;349:179.
11. Strobel S, Morgan G, Simmonds AH, Levinsky RJ. Fatal graft versus host disease after platelet transfusions in a child with purine nucleoside phosphorylase deficiency. Eur J Pediatr. 1989;148:312-4.
12. van Royen-Kerkhof A, Wulffraat NM, Kamphuis SS, Brooimans RA, de Weger RA, Tilanus MG, van Leeuwen EF, Rijkers GT. Nonlethal transfusion associated graft-versus-host disease in a severe combined immunodeficient patient. Bone Marrow Transplant. 2003;32:1027-30.
13. BCSH Blood Transfusion Task Force. Guidelines on gamma irradiation of blood components for the prevention of transfusion-associated graft-versus-host disease. Transfus Med. 1996;6:261-71.

Manuscript received April 8, 2009; accepted for publication, July 14, 2009.

Sara Sebnem Kilic

Uludag University Medical Faculty
Department of Pediatric Immunology
Gorukle- Bursa 16059, Turkey
E-mail: sebnemkl@uludag.edu.tr

